Treatment of Patients with Metastatic Melanoma by Lymphodepleting Conditioning Followed by Infusion of TCR-Gene Engineered Lymphocytes and Subsequent Peptide Immunization

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Non-Technical Abstract:

This study will be performed in patients who have metastatic melanoma. The main purpose of this research study is to determine whether special tumor fighting cells that we take from patients' blood or tumors, introduce genetic material called anti-melanoma protein TCR retroviral vector and grow in the laboratory, and then give back to the patient, will improve the ability to fight the patients' cancer when we suppress their immune system from attacking these special tumor fighting cells. The two anti-melanoma proteins we will use are gp100 and MART-1. The secondary objectives of this study are to determine the survival of infused cells that have been retrovirally transduced to be reactive with melanoma tumor antigens gp100 or MART-1 and to determine the toxicity of the treatment.

Initially patients will have lymphocytes harvested either through leukopheresis or a biopsy of their tumor. The lymphocytes will be grown in the laboratory.. During the procedure to grow the cells in the laboratory, a piece of genetic material, the anti-melanoma protein (gp100 or MART-1) T-cell receptor (TCR) will be put into the cells using a process called "retroviral transduction". The retrovirus is made from a virus that has been inactivated or changed in a way that prevents it from reproducing and causing any type of illness. It serves only as a vehicle to deliver the anti-melanoma protein TCR into the cells. Since we do not know which anti-melanoma protein will work best, patients will be randomly assigned to have their lymphocytes transduced with either the anti-gp100 TCR retroviral vector or the anti-MART-1 TCR retroviral vector. Up to 17 patients will be assigned to each vector group.

Once the cells are grown in the laboratory and the gene inserted, patients will be given chemotherapy, (cyclophosphamide and fludarabine) for seven days to suppress the immune system. On the eighth day, they will be given two injections of the melanoma peptide corresponding to the melanoma protein used to engineer their cells, either

gp100:209-217(210M) or MART-1:26-35(27L), emulsified in an immune-stimulating adjuvant, Montanide ISA-51, in an effort to increase the immune response. These injections will be repeated for five days and then weekly for 3 more injections for a total of eight days of injections. On the eighth day, all patients will be given the cells intravenously, over 20-30 minutes, followed within 24 hours with intravenous Interleukin 2 (IL-2, a hormone that stimulates lymphocyte growth) at 720,000 IU/kg every 8 hours for up to 15 doses, depending on patient tolerance. Patients will be given appropriate medications to treat the side effects of this treatment regimen and to prevent infection secondary to the immune suppression caused by the chemotherapy.

Patients will return to NIH after four to six weeks to have their tumor(s) evaluated. If there is shrinkage of their tumor(s), the cell infusion will be repeated. If there is no response, patients will be taken off this study. In patients who are responding, up to one retreatment course may be given.